eaten a sufficient amount of food, it would seem that further exploration of the appropriateness of this reference base is in order.

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Atypical Measles Syndrome: A Continuing Problem

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Atypical measles syndrome (AMS), first described in 1965 by Rauh and Schmidt[1], is characterized by high fever, unusual rash, and pneumonia, often with a history of immunization with killed measles vaccine. AMS is generally thought to be a hypersensitivity response to natural measles infection in individuals who have previously received killed measles vaccine,[2–10] although several investigators have reported AMS-like illness in children who had been immunized only with live measles vaccine.[11, 12] These latter reports may be misleading since it is sometimes clinically difficult to distinguish typical from atypical measles.

During a measles epidemic in 1974–1975 in Northern California, a number of physicians reported laboratory-confirmed measles in patients who had signs and symptoms compatible with AMS. We investigated these cases to clarify the epidemiology of AMS and its association with previous measles immunization. Two of the cases have been reported.[13]

Materials and Methods

Measles surveillance in California has relied primarily on case reporting by physicians and school nurses; clinical data are not included with these reports. For this study, we reviewed records of the state and county public health viral diagnostic laboratories for 1974 and 1975 to identify possible AMS cases. We developed case criteria on the basis of serology and rash distribution and morphology. In typical measles a maculopapular rash occurs first at the hairline, progresses caudally, is concentrated on the face and trunk, and is often accompanied by Koplik's spots. In AMS the rash is morphologically a mixture of maculopapular, petechial, vesicular, and urticarial components; if usually begins and is concentrated primarily on the extremities, progresses cephalad, and is not accompanied by Koplik's spots. Cases were classified as AMS if patients had: 1) a rash with the distribution and morphology characteristic of AMS, and 2) a fourfold or greater rise in titer of complement-fixing measles antibody or a convalescent titer of $\geq$256.

Laboratory record review revealed 270 reports with positive serologic results and clinical findings suggesting an unusual clinical presentation of measles. Referring physicians were contacted to obtain additional details, including a measles immunization history.

Results

Fifty-six of the 270 cases (20 per cent) met our criteria for AMS: 35 cases were in males and 21 in females. Age-specific incidence of AMS differed from that for the routinely reported measles cases in California in 1974–1975 (Figure 1). Over 90 per cent of AMS cases were in adolescents, with peak incidence in those aged 10–14 years, whereas peak occurrence for all reported measles cases was in the five- to nine-year age group.

Of the 56 AMS patients, 50 (89 per cent) had a medical record of having received measles vaccine (Table 1), and all but one of this latter group had received killed vaccine. Twenty-eight patients had received two or more doses of killed vaccine followed by live vaccine, and 26 of these had

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TABLE 1—Measles Immunization History of 56 Cases of Atypical Measles, California, 1974-1975

Vaccine(s) Received	Number of Patients	Percentage of Total
Killed and Live Vaccine	32	57
Killed Vaccine—Live Vaccine Uncertain	7	12
Killed Vaccine Only	10	18
Live Vaccine Only	1	2
Vaccine Type(s) Uncertain	6	11
TOTAL	56	100

received live vaccine within three months after the last dose of killed vaccine. The longest interval from immunization with killed measles vaccine to onset of AMS was 12 years, 5 months; the mean interval was 10 years, 6 months. At least four cases received only one dose of killed vaccine followed by a dose of live vaccine.

AMS was diagnosed by the patients' physicians in only 17 (30 per cent) of the 56 cases.*

The average number of days from prodrome onset to rash was three and one-half days. The rash began on the extremities in 36 cases and on the face in only two cases; it was concentrated on the extremities and, in nearly all cases, had petechial, urticarial, and/or vesicular components. Of 44 patients with chest radiographs, 41 had pulmonary infiltrates, 10 had mediastinal adenopathy, and seven had pleural effusion. These abnormalities persisted in some cases for many weeks. Forty-two patients were hospitalized and, although none died, many were severely ill.

Virus isolation was attempted unsuccessfully in 19 cases. Bacterial cultures were reported as negative. Ten of the patients had eosinophilia.

Discussion

The clinical, laboratory, and radiologic characteristics of our case series are consistent with those in previous AMS case reports.[1-10, 14] As far as we are aware, however, there have been no previous reports of an unequal sex ratio for those who develop AMS. The male/female ratio is 1.7 in our study group; this finding may reflect the frequently observed male preponderance noted in many other infectious diseases, may be due to sampling variation, or could mean that more males than females were immunized with killed measles vaccine.

The 56 AMS cases in our series support the generally accepted view that some children immunized with killed measles vaccine contract AMS in succeeding years if exposed to measles virus. Fulginiti suggested that the response of recipients of killed measles vaccine to the natural virus depends on the level of serum antibody and the persistence of delayed hypersensitivity induced by the killed vaccine.[4] He suggests that the serum antibody level is high enough to be fully or partially protective initially following immunization. After several years, serum antibody may fall to very low levels, while delayed hypersensitivity persists. The recipient, no longer protected against measles, may develop atypical measles if exposed. Fulginiti postulated that two-thirds of killed vaccine recipients are susceptible to AMS five- to six-years after immunization.[9] Our findings indicate that the hypersensitivity response persists for 10 to 12 years after immunization with killed vaccine. A duration of 14 years was recently reported by Haas and Wendt.[15] Our findings also indicate that only one dose of killed vaccine can predispose to AMS.

About 1,836,000 doses of killed measles vaccine were distributed in the United States between 1962 and 1967.[7] Since most individuals received two or three doses of killed vaccine, it is probable that 600,000-900,000 children received some killed vaccine, some of whom may remain susceptible to AMS at least through the 1970s and perhaps longer.

One of our 56 patients had received only live vaccine. In several respects, however, this child's illness did not fit the clinical pattern seen in cases associated with killed vaccine. The lesions of the rash were macular, not raised, involved his lips, and suggested iris lesions more compatible with the diagnosis of erythema multiforme. Even if this case were considered to be AMS, the incidence of AMS associated with live measles vaccine remains extremely low.

Of the 28 patients who had a history of receiving both killed and live measles vaccine, all but two received live measles vaccine within three months after receiving killed measles vaccine. These findings support the recent recommendation of the U.S. Public Health Service's Advisory Committee on Immunization Practices: "Despite the risk of local reaction, children who have previously been given inactivated vaccine alone or followed by live vaccine within three months should be revaccinated with live vaccine to

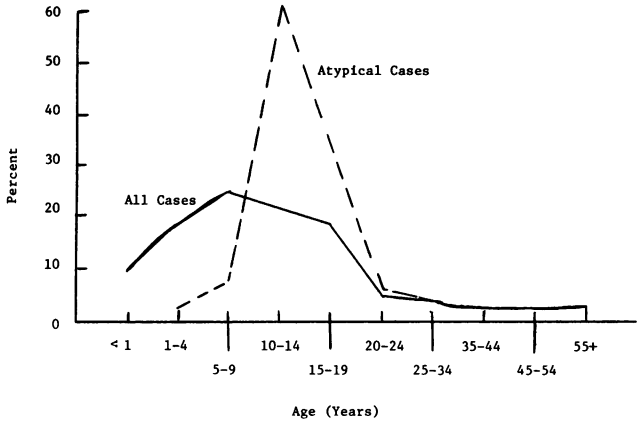

FIGURE 1—Percentage of Measles Cases by Age, California, 1974-1975

*The other diagnoses included "viral syndrome—type unknown" (17 cases), pneumonitis of unknown etiology (5), Rocky Mountain spotted fever (5), influenza (5), staphylococcal pneumonia (2), fever of unknown origin (2), varicella (1), erythema multiforme (1), and pharyngitis (1).

avoid the severe atypical form of natural measles and to provide full and lasting protection."[16]

It may be difficult to identify persons who have received killed measles vaccine. If good records are not available to indicate otherwise, individuals receiving more than one dose of measles vaccine two weeks to several months apart (not simultaneously) prior to 1968 were probably given killed measles vaccine and should now be given live measles vaccine.

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